REMARKS

Claims 1-34 are pending and claims 3-4, 18-21, 29-32 and 34 are currently under examination. By the present communication claim 30 has been cancelled, claims 3, 29, 31, 32 and 34 have been amended, and new claim 35 has been added. Claims 29, 31 and 34 have been amended to recite a B cell, support for which can be found throughout the specification including, for example, on page 23, lines 25-30 and page 28, lines 13-30. Claims 29 and 32 have been amended to recite administering to an individual and claim 34 has been amended to recite that the nucleic acid molecule is administered to the lymphoid tissue and targeted to a cell *ex vivo*, and said targeted cell is administered to an individual. Support for the amendments to claims 29, 32 and 34 can be found throughout the specification including, for example, on page 58, line 12, through page 59, line 9. Claims 3 and 29 have been amended to recite that the one or more heterologous epitopes or the polypeptide is expressed in a B cell, support for which can be found in the specification including, for example on page 23, lines 25-30 and page 33, lines 7-23. Support for new claim 35 can be found in the specification including, for example, in claims 1 and 4 as originally filed, on page 23, lines 25-30; page 33, lines 7-23; and page 58, line 1, through page 59, line 9. Accordingly, the amendments and new claims do not introduce new matter and entry thereof is respectfully requested.

Applicant has set forth above the amended claims in clean form as required under 37 C.F.R. § 1.121(c)(i). Applicant

also attach the appendix "Marked Up Claim Amendments" with the claim amendments indicated with brackets and underlining as required under 37 C.F.R. § 1.121(c)(ii).

Rejection under 35 U.S.C. § 112, first paragraph

The rejection of claims 3, 4, 18-21, 29-32 and 34 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed. Applicant respectfully submits that the specification provides sufficient description and guidance to enable the full scope of the claimed methods and compositions. More specifically, the specification is enabling for claim 3 which, as amended, is directed to a method for stimulating an immune response by administering to a lymphoid tissue a nucleic acid molecule containing an expression element operationally linked to a nucleic acid sequence encoding one or more heterologous epitopes, wherein the expression element includes a B cell expression element and wherein the one or more heterologous epitopes are expressed in a B cell. The specification also provides sufficient description and guidance to enable claim 18 which is directed to a nucleic acid molecule having a B cell expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide, wherein the B cell expression element includes a B cell promoter and enhancer. The specification further provides sufficient description and guidance to enable claim 29 which, as amended, is directed to a method of treating a condition by administering to an individual a nucleic acid molecule containing a B cell expression element operationally linked to a nucleic acid

sequence encoding a heterologous polypeptide, wherein the heterologous polypeptide is expressed in a B cell.

In regard to the use of cytokines in the claimed methods, Applicant respectfully maintains that the specification is enabling for the claimed methods of treating a condition by administering to an individual a nucleic acid molecule comprising a B cell expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide, wherein said heterologous polypeptide is expressed in a B cell. The teaching in the specification of performing the methods by also administering a cytokine is merely exemplary of particular embodiments of the claimed methods for achieving greater modulation of a particular immune response. However, the specification also teaches that the claimed methods can be performed to treat a condition absent addition of a cytokine, as set forth below.

The specification demonstrates use of the claimed methods to treat influenza, absent addition of cytokines, in Example IX. A nucleic acid molecule having a B cell expression element operationally linked to a sequence encoding thirteen amino acid residues of an influenza virus nucleoprotein antigen was administered to mice according to the claimed methods (see page 123, line 1, through page 124, line 3). A majority of the DNA-immunized mice (60-75%) generated a cytotoxic T- cell response specific for the influenza NP protein (see page 125, lines 5-13) and a majority of the DNA-immunized mice (50-60%) survived a dose of influenza virus that killed non-immunized

control mice within 11 days (see page 125, lines 15-26 and Figure 34). The specification also demonstrates that addition of cytokines was not necessary for activation of CD4 T cells against determinants of a tumor antigen in Example X. A nucleic acid molecule having a B cell expression element operationally linked to a sequence encoding two amino acid sequences from the tandem repeat of the tumor antigen MUC-1 and a Th cell determinant from the outer coat of *P. Falciparum* was administered according to the claimed methods (see page 126, lines 4-19). Mice immunized with the nucleic acid mounted a strong T cell proliferative response to the MUC-1 epitope (see page 126, lines 21-32 and Figure 36).

Furthermore, Applicant respectfully disagrees with the assertion in the Office Action that the specification teaches on page 109 that in the absence of GM-CSF, the IgG1 antibody titer generated by g1NANP alone does not appear to be immunologically relevant. The mere teaching of an increased antibody titer for mice primed with DNA in the presence of GM-CSF compared to in the absence of GM-CSF does not teach or even appear to teach that the lesser antibody titer was immunologically irrelevant. Rather, the results described on page 109 indicate that use of the claimed methods, absent administration of a cytokine, yielded an antibody titer of Log 4.1. Similarly, although the specification teaches on page 102, lines 19-23, that inoculation with DNA/IL-2 did not yield a primary antibody response that was greater than that seen with DNA alone, the DNA/IL-2 inoculation was able to induce a primary antibody response as demonstrated by Figure 20A and Figure 21. Thus, the specification teaches that cytokines are not necessary to treat a condition or to stimulate an immune

response using the claimed methods and that cytokines can be used to increase a particular immune response where desired.

Applicant respectfully maintains that the specification provides sufficient enablement for stimulating an immune response against a variety of conditions and for treating a variety of conditions with the claimed methods. The specification teaches the stimulation of an immune response against *P. falciparum* malaria sporozoites, as acknowledged in the Office Action. The specification further teaches stimulating an immune response to influenza (see, for example, page 123, line 1, through page 125, line 13) and to mount a strong T cell proliferative response to the MUC-1 tumor epitope (see page 126, lines 4-32). Moreover, those skilled in the art would have recognized that immunological protection against antigens of *P. falciparum* malaria sporozoites and influenza virus as demonstrated by protection from challenge with *P. falciparum* and influenza virus, respectively, as well as an immune response to MUC-1 are model systems yielding representative results for a variety of antigens representing diverse pathological conditions, including, for example, a virus, tumor or parasite.

Applicant respectfully maintains, for the reasons of record, that the specification is enabling for the claimed methods and compositions reciting a nucleic acid molecule comprising a hematopoietic cell expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide. Nevertheless, in order to further prosecution of this application claim 29 has been amended to recite a nucleic

acid molecule comprising a B cell expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide. Therefore, the rejection of claims 29-32 regarding the recited hematopoietic cell expression element is rendered moot.

Furthermore, Applicant respectfully disagrees with the assertion in the office Action that the specification fails to teach any promoter element other than the immunoglobulin heavy chain promoter/enhancer. The specification teaches a variety of promoter elements including, for example, hematopoietic cell expression elements that function in B cells, T cells or dendritic cells as taught on page 28, lines 13-30. Moreover, the claims, as amended, recite a B cell expression element. Use of B cell expression elements in the methods and compositions of the invention is taught in the specification including, for example on page 33, lines 8-22, which teaches administration of a nucleic acid having B cell expression elements for expression of the nucleic acid in B lymphocytes.

Applicant respectfully submits that any alleged unpredictability with respect to expression of a gene using any vector using any promoter element or alleged unpredictability of targeted gene delivery is not relevant to the claims. The method claims, as amended, recite that the one or more heterologous epitope or heterologous polypeptide is expressed in a B cell. Furthermore, the specification provides examples of the expression of various antigens using B cell expression elements

and the claims specifically recite that the heterologous epitope is expressed in a B cell.

Moreover, the specification is enabling for methods of stimulating an immune response or treating a condition where one or more heterologous epitope or heterologous polypeptide is expressed in a B cell. As set forth above, the specification demonstrates use of the claimed methods to treat influenza and to mount a strong T cell proliferative response to the MUC-1 tumor epitope. In addition, the specification demonstrates that a single administration of a nucleic acid containing a B cell expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide is sufficient to initiate immunity (see Example I), establish immunologic memory (see Example V), and program the immune response predictably and reproducibly (see Examples II and IV). The specification demonstrates that B lymphocytes are the target cell population of the nucleic acid as demonstrated by PCR-amplification of genomic DNA from purified B cells (see Example II). After a single administration to the spleen, the transgene persisted functionally for four months as demonstrated in Example II. This persistence of the transgene indicates that the cells transfected *in vivo* were long-lived B lymphocytes as taught on page 44, lines 28-31 of the specification.

The specification further demonstrates in Example III that a single administration of a nucleic acid containing a B cell expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide allows the immune

system to be programmed for the production of anti-parasite antibodies in all mice tested. Example III further demonstrates that immunologic memory was established as revealed by booster with an antibody antigenized with the NANP peptide administered in adjuvant or through challenge with the parasite. In view of the teaching and guidance provided in the specification, those skilled in the art would have recognized that the claimed methods can be used as an effective approach for vaccination in treating a variety of conditions and against a variety of antigens.

Applicant respectfully submits that in view of the teaching and guidance provided in the specification, those skilled in the art would have been able to administer the claimed nucleic acids to a variety of lymphoid tissues *in vivo* or *ex vivo* including, but not limited to the spleen, in order to stimulate an immune response or treat a condition according to the claimed methods. The specification teaches that the claimed methods can include administering a nucleic acid to a number of lymphoid tissues including, for example, spleen, lymph nodes, mucosa-associated lymphoid tissue (MALT), including tonsils and Payer's patches, and the nasal-associated lymphoid tissue (NALT) such as the Waldeyer's ring, and the urogenital lymphoid tissue (see page 26, lines 24-31). A nucleic acid can be administered to lymphoid tissues according to methods taught in the specification including, for example, direct injection into a lymphoid tissue such as a lymph node or spleen (see page 26, line 31, through page 27, line 30). In view of the teaching provided in the specification, those skilled in the art would have expected that administering a nucleic acid having a B cell expression element

operationally linked to a nucleic acid sequence encoding a heterologous polypeptide or epitope to a lymphoid tissue other than the spleen would result in stimulation of an immune response since the lymph node contains a sufficient number and concentration of B cells for stimulation of an immune response or for treating a condition following administration of the claimed nucleic acid molecule according to the claimed methods.

As set forth above, the claims as amended are enabled by the specification. Accordingly, Applicant respectfully requests that this ground for rejection be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Applicant respectfully traverses the rejection of claims 32 and 34 as allegedly indefinite. Those skilled in the art would have understood from the teaching provided in the specification that a method of stimulating an immune response or treating a condition, which includes *ex vivo* targeting would include administering the *ex vivo* targeted cell to an individual. Nevertheless, in order to further prosecution of this application, claims 32 and 34 have been amended to specifically recite the step of administering the *ex vivo* targeted cell. Thus, claims 32 and 34, as amended, are sufficiently clear. Accordingly, Applicant respectfully requests that this ground for rejection be withdrawn.

Rejection under 35 U.S.C. § 102(b)

The rejection of claims 18 and 19, under 35 U.S.C. § 102(b), as allegedly anticipated by Banerji et al., Cell 33:729-740 (1983), is respectfully traversed. The plasmids described in the reference by Banerji et al. and shown in Figure 1 contain the SV40 early promoter, a rabbit beta globin gene, SV40 sequences coding for T-antigen and either no enhancer, an immunoglobulin enhancer or an SV40 enhancer. The results shown in Figure 2 of Banerji et al. were obtained with HeLa cells or myeloma cells transfected with plasmids expressing T-antigen under the control of the SV40 promoter in combination with either no enhancer (left panel), the immunoglobulin enhancer (middle panel), or the SV40 enhancer. In contrast, claims 18 and 19 are directed to a nucleic acid molecule containing a B cell expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide, wherein the B cell expression element includes a B cell promoter and enhancer. Nowhere does Banerji et al. describe a nucleic acid molecule containing both a B cell promoter and enhancer. Therefore, the reference by Banerji et al. does not anticipate claims 18 and 19. Accordingly, Applicant respectfully requests that this ground for rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a)

The rejection of claims 3, 4, 18, 19 and 29-31, under 35 U.S.C. § 103(a), as allegedly obvious over Hurpin et al. Vaccine 16:208-215 (1998) in view of Banerji et al., is

respectfully traversed. Applicant respectfully submits that the references, taken alone or in combination, do not teach or suggest the claimed compositions and methods, as set forth below.

Composition claims 18 and 19 are directed to a nucleic acid molecule containing a B cell expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide, wherein the B cell expression element comprises a B cell promoter and enhancer. As acknowledged on page 10, lines 19-20 of the Office Action, Hurpin et al. does not specifically teach the use of a B cell specific promoter. Banerji et al. does not cure the deficiencies of Hurpin et al. because, as set forth above in response to the rejection under 35 U.S.C. § 102(b), Banerji et al. does not teach a nucleic acid molecule containing a B cell promoter. Applicant respectfully submits that Hurpin et al. or Banerji et al. taken alone or in combination do not teach or suggest a nucleic acid molecule containing a B cell promoter. Therefore, claims 18 and 19 are not obvious over Hurpin et al. in view of Banerji et al.

In regard to method claims 3, 4 and 29-31, Applicant respectfully submits that the description in Hurpin et al. and Banerji et al., taken alone or in combination, would not have motivated one of ordinary skill in the art to stimulate an immune response or treat a condition by administering a nucleic acid containing a B cell expression element operationally linked to a nucleic acid sequence encoding a heterologous epitope. Hurpin et al. describe intrasplenic administration of a vector expressing p53 under the control of a CMV promoter as inducing CTLs at

similar levels to those achieved by intravenous administration (see the sentence spanning pages 210 and 211). The description of satisfactory induction of CTLs using the vector of Hurpin et al. would not have motivated one skilled in the art to alter the vector in any way, much less by incorporating a B cell expression element. Banerji et al. do not cure the deficiencies of Hurpin et al. Although Banerji et al. describe increased expression for a plasmid incorporating an immunoglobulin enhancer, Banerji et al. do not suggest any advantage to further increasing expression of p53 over the satisfactory levels achieved by Hurpin et al. Absent suggestion of any need or advantage to increase the expression of p53 in the methods of Hurpin et al., one skilled in the art would not have been motivated to alter the vector of Hurpin et al. to incorporate any other expression element, much less a B cell expression element.

Even if, for the sake of argument, Hurpin et al. and Banerji et al. were construed to provide any motivation to alter the vector described by Hurpin et al., the references taken alone or in combination would not have provided motivation to incorporate a B cell expression element in the vector. There is no teaching or suggestion in Hurpin et al. or Banerji et al. of expressing a heterologous epitope in a B cell. In regard to the assertion in the Office Action that the spleen contains a large percentage of B cells, Applicant respectfully submits that the spleen was known to contain a variety of other antigen presenting cells including, for example, dendritic cells and macrophages. It is only with the benefit of hindsight that any motivation can

be found for targeting B-cells from the mere description of intrasplenic administration by Hurpin et al.

Indeed, it is well settled that Applicants' disclosure cannot be used to hunt through the prior art for the claimed elements and then combine them as claimed (In re Laskowski, 871 F. 2d 115, 117, 10 USPQ 2d 1397, 1398 (Fed. Cir. 1989). Hindsight cannot be used to resolve the question of obviousness (Orthopedic Equipment Co., Inc. v United States, 702 F.2d 1005, 1012 (Fed. Cir. 1983)):

> [t]he difficulty which attaches to all honest attempts to answer this question [non-obviousness] can be attributed to the strong temptation to rely on hindsight while undertaking this evaluation. It is wrong to use the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.

The mere description in Hurpin et al. of intrasplenic administration does not teach or suggest targeting a B cell over any other antigen presenting cell in the spleen. Absent Applicant's teaching in the instant application of targeting B cells as powerful minifactories of antigenic material, exploiting the natural high level expression of immunoglobulins in B cells, no motivation exists in the art of record to target a B cell over any of the other antigen presenting cells of the spleen. Thus, it is only with the hindsight benefit of Applicant's disclosure that the combination of references can be advanced. Such

hindsight application of Applicant's disclosure is clearly improper.

Hurpin et al. or Banerji et al., taken alone or in combination, does not teach or suggest Applicant's claimed invention. Accordingly, Applicant respectfully requests that this ground for rejection be withdrawn.

CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

January 22, 2002
Date

Deborah L. Cadena
Registration No. 44,048
Telephone No. (858) 535-9001
Facsimile No. (858) 535-8949

CAMPBELL & FLORES LLP
4370 La Jolla Village Drive
7th Floor
San Diego, California 92122
USPTO CUSTOMER NO. 23601

APPENDIX A

Marked up claim amendments.

3. (Amended) A method for stimulating an immune response, comprising administering to a lymphoid tissue a nucleic acid molecule comprising an expression element operationally linked to a nucleic acid sequence encoding one or more heterologous epitopes, wherein said expression element comprises a B cell expression element and wherein said one or more heterologous epitopes are expressed in a B cell.

29. (Amended) A method of treating a condition, comprising administering to an individual a nucleic acid molecule comprising a B [hematopoietic] cell expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide, wherein said heterologous polypeptide [nucleic acid molecule] is expressed in [targeted to] a B [hematopoieitc] cell.

31. (Amended) The method of claim 29, wherein said B [hematopoietic] cell is targeted *in vivo*.

32. (Amended) The method of claim 29, wherein said B [hematopoietic] cell is targeted *ex vivo* and then administered to said individual.

34. (Amended) The method of claim 3, wherein said nucleic acid molecule is administered to said lymphoid tissue and targeted to a cell *ex vivo*, and said targeted cell is then administered to an individual.

COPY OF PAPERS
ORIGINALLY FILED